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STAGE AT DIAGNOSIS IS A KEY EXPLANATION OF DIFFERENCES IN BREAST CANCER SURVIVAL ACROSS EUROPE

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We used multiple regression models to assess the influence of disease stage at diagnosis on the 5-year relative survival of 4,478 patients diagnosed with breast cancer in 1990–1992. The cases were representative samples from 17 population-based cancer registries in 6 European countries (Estonia, France, Italy, Netherlands, Spain and UK) that were combined into 9 regional groups based on similar survival. Five-year relative survival was 79% overall, varying from 98% for early, node-negative (T1N0M0) tumours; 87% for large, node-negative (T2-3N0M0) tumours; 76% for node-positive (T1-3N+M0) tumours and 55% for locally advanced (T4NxM0) tumours to 18% for metastatic (M1) tumours and 69% for tumours of unspecified stage. There was considerable variation across Europe in relative survival within each disease stage, but this was least marked for early node-negative tumours. Overall 5-year relative survival was highest in the French group of Bas-Rhin, Côte d'Or, Hérault and Isère (86%), and lowest in Estonia (66%). These geographic groups were characterised by the highest and lowest percentages of women with early stage disease (T1N0M0: 39% and 9%, respectively). The French, Dutch and Italian groups had the highest percentage of operated cases. The number of axillary nodes examined, a factor influencing nodal status, was highest in Italy and Spain. After adjusting for TNM stage and the number of nodes examined, survival differences were greatly reduced, indicating that for these women, diagnosed with breast cancer in Europe during 1990–1992, the survival differences were mainly due to differences in stage at diagnosis. However, in 3 regional groups, the relative risks of death remained high even after these adjustments, suggesting less than optimal treatment. Screening for breast cancer did not seem to affect the survival patterns once stage had been taken into account.

Key words: *breast cancer; population registries; care; survival; Europe*

The EUROCARE study of the survival and care of cancer patients in Europe has shown marked variations in survival from breast cancer,[1,2] with highest survival in Nordic countries (Sweden, Finland, Iceland and Norway) and lowest survival in the countries of the former Eastern bloc. Low survival was also found in the UK and Denmark. These survival differences are not easily interpreted. Longer survival could be due to better treatment, more effective treatment due to diagnosis at earlier stage or simply to early diagnosis without any advantage to the patient (lead-time bias). In a previous study designed to explain these regional differences, we analysed detailed diagnostic and therapeutic information on samples of breast cancer patients diagnosed in 1990–1991 who were recorded in cancer registry files. We found differences between the cancer registry areas in stage at diagnosis that were related to the overall survival differences.[3]

Regional survival differences should therefore diminish if appropriate stage-adjusted comparisons are performed. However, stage is highly sensitive to the diagnostic procedures used to define it, and the thoroughness of the investigations performed, particularly those capable of revealing occult metastases.[4] As a consequence, tumours classified as "localised" in an area where intensive diagnostic investigations are usually performed are likely to be more localised than tumours assigned the same stage in another area where investigations are (for whatever reason) less thorough. The corollary is that the survival of "localised" cases will be better in the area of intensive investigation, simply because of a different de facto definition of stage at diagnosis, and not because of better treatment. Furthermore, "advanced" cases will also have better survival in the area of intensive investigation because of the

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inclusion of some less advanced metastatic cases in this category that would be classified as "localised" in the area of less thorough investigation.[5] Stage-adjusted survival comparisons should, therefore, take into account the diagnostic examinations used to define the stage.

The aim of our study is to present stage-specific 5-year relative survival for breast cancer from selected European cancer registries, and to analyse the effects of disease stage at diagnosis, age, general mortality and the number of nodes examined during lymphadenectomy using a multivariate regression model to assess the influence of all these factors on survival. The number of axillary lymph nodes examined pathologically was 1 of the most important determinants of breast cancer stage during the early 1990s.

The results should make it possible to interpret the differences in breast cancer survival across Europe. Survival differences that persist after adjustment for tumour stage at diagnosis are more likely to be due to differences in treatment or to differences in tumour biology. We have performed a similar analysis of the survival of colon cancer patients in Europe.[6]

MATERIAL AND METHODS

Seventeen population-based cancer registries from 6 European countries (Estonia, France, Italy, Netherlands, Spain and UK) participating in EUROCARE adhered to a common protocol for investigating the diagnostic and therapeutic procedures used for treating breast cancer. Each registry provided a representative sample of breast cancer cases diagnosed in 1990 (1991 for Estonia and Netherlands) or during the period 1990–1992 for the smallest cancer registry (Ragusa, Southern Italy). Detailed clinical information on each case was subsequently abstracted from the clinical notes by trained personnel.

The participating cancer registries were asked to provide data on all cases of invasive breast cancer, or a representative sample thereof, diagnosed in 1990. At least 200 cases per registry were required; if this minimum was not reached in 1990, the study period was prolonged until 200 cases were accrued. A total of 4,478 breast cancer cases were analysed. Data collection was considered complete when, for each registry, the number of cases collected by the trained personnel was equal to the total number of incident cases in the registry records. Extensive details of the study design and inclusion criteria are included in the first descriptive analysis.[3]

Most of the clinical items requested were available in the primary treatment clinical records. However, in some registries, extent of disease at diagnosis was not available for many cases and had to be reconstructed by examining other clinical records in addition (e.g., pathology reports and discharge records).

Extent of disease at diagnosis was categorized according to TNM rules (3rd edition).[7] Pathologic T and N categories were used for women who underwent surgery, and clinical information on T, N and M was used for those not treated surgically. We present the cancer registry data by country and, within France, Italy and the UK, for groups of 1 or more regional registries defined by similar survival and stage distribution at diagnosis. Thus, for Italy, the registries of Varese, Firenze and Modena, in the northern part of the country, were grouped together; while Ragusa in south-eastern Sicily was kept separate. Two groups with similar survival were identified in France, the first comprising the registries of Bas-Rhin, Côte d'Or, Hérault and Isère; the second those of Tarn, Somme, Calvados and Doubs. In the UK, the registries of Thames and Mersey were kept separate, as they differed considerably in the distribution of stage at diagnosis and in breast cancer survival.

Each individual registry used its own follow-up procedures. The UK registries updated the life status of patients included in our study, linking death certificates of the general population to the registry records; all the other registries performed an active search of the life status of their patients using various sources of information (e.g., registry of general practitioners, municipality files). At least 5 years' follow-up information was available for all women. For patients included in the first EUROCARE study, diagnosed in 1978–1985, we performed an extensive follow-up quality study of long-surviving cases in registries that employed passive follow-up procedures. We found that the small number of errors uncovered in terms of life status did not affect survival estimates.[4] Comparison of registry-specific 5-year relative survival of cases included in our study with that of the Eurocare-2 project, including patients diagnosed in 1985–1989, revealed satisfactorily consistent survival levels, indicating that the quality of follow-up for the patients in the present study was high.[3]

Relative survival, expressing the probability of cancer survival after adjustment for competing causes of death, was estimated as the ratio of the observed survival to the expected survival based on the age- and sex-specific mortality rates of the general population from which the cancer cases were drawn. Overall and stage-specific 5-year relative survival rates were calculated by the Hakulinen method[8] using general population life tables specific for each registry region.

For the univariate analysis, stage was assigned to 1 of 5 categories: small, node-negative (T1N0M0); large, node-negative (T2-3N0M0); node-positive (T1-3N+M0, regardless of the number and anatomic level of the involved nodes in the axilla); locally advanced (T4NxM0, large tumours with skin/chest wall involvement, regardless of nodal status); metastatic (M1) and of unspecified stage.

Geographic differences in 5-year relative survival were modelled using a recently developed multiple regression approach based on generalised linear models and adopting the Poisson assumption for the observed number of deaths.[9] The relative excess risks (RERs) derived from these models quantify the extent to which the hazard of death in a given area (age group, etc.) differs from the hazard in the reference category after taking into account the overall risk of death in the general population.

In these models, age at diagnosis was categorized into < 40 years, 40–49, 50–69 and 70 years or more (reference category) because these age ranges correspond to different hormone patterns associated with different prognosis, and because screening for breast cancer is usually carried out after age 50. Surgical treatment of the breast was included in the model regardless of the type of surgery.

The 3 components of disease stage, T, N and M, were modelled separately to estimate the independent prognostic value of each, adjusted for all the other factors included in the analysis. Tumour size was divided into 4 categories (T1–T4, according to TNM rules), with T1 as reference. Nodal status was categorised by the number of metastatic nodes, divided into 10 categories, with no positive nodes (N0) as the reference group, and additional categories for clinically node-negative cases, nodal metastases with an unknown number of involved nodes and nodal status unknown. The number of metastatic nodes was chosen as an indicator of nodal stage because it is itself a prognostic indicator,[10–12] and because the number of metastatic nodes was more widely available in participating cancer registries than the standard N categories based on TNM rules. The probability of detecting nodal metastases is directly related to the number of axillary nodes examined pathologically. The number of lymph nodes examined was therefore also included in the models as a determinant of nodal status, categorised into tertiles, with a fourth category for cases where the axilla was not examined surgically; a few cases for which this information was not available were grouped with the last category.

RESULTS

Table I shows the total number of cases by country and regional group, with information on treatment, stage and staging procedures influencing N stage. More detailed information on stage at diagnosis and treatment of these patients has been published.[3]

During the study period, organised breast cancer screening was in place in the UK and in the French regions of Bas-Rhin, Hérault and

TABLE I – STAGE, STAGING INVESTIGATIONS, SURGERY AND LOSS TO FOLLOW-UP OF WOMEN DIAGNOSED WITH BREAST CANCER 1990–1992 FROM SELECTED EUROPEAN GEOGRAPHIC GROUPS

Country	Regional group	Number of women	Operated patients (%)	Axillary dissection (%)[1]	10 or more nodes examined (%)[2]	% lost to follow-up
Italy	Varese, Firenze, Modena	976	93.1	85.9	77.2	0.8
Italy	Ragusa	217	87.5	80.6	71.4	0.0
France	Bas-Rhin[3], Côte d'Or, Hérault[3], Isère[3]	865	92.9	89.5	57.5	5.6
France	Tarn, Somme, Calvados, Doubs	949	91.1	86.6	60.7	5.3
Spain	Granada	179	88.3	79.9	82.5	5.0
Estonia		224	74.5	69.6	3.2	4.9
UK	Thames[3]	340	83.2	50.0	25.9	0.9
UK	Mersey[3]	219	87.6	49.8	18.3	0.0
NL	Eindhoven	509	92.7	86.6	51.1	0.0
All cases		4,478	90.2	81.0	58.7	3.0

[1]Percentage of all women.–[2]Percentage of women who underwent axillary lymphadenectomy.–[3]Organized mass screening in place during the study period.

TABLE II – 5-YEAR RELATIVE SURVIVAL (%) BY STAGE AND GEOGRAPHIC AREA OF WOMEN DIAGNOSED WITH BREAST CANCER 1990–1992 FROM SELECTED EUROPEAN REGIONAL GROUPS

Country	Regional group		T1 N0 M0	T2–3 N0 M0	T1–3 N+ M0	T4 Nx M0	M1	Not known	Overall
Italy	**Varese, Firenze, Modena**	**5-year survival (%)**	**97.2**	**92.4**	**78.7**	**59.7**	**22.7**	**61.1**	**82.1**
		Frequency (%)	30.5	19.2	31.4	6.7	5.6	6.6	100
Italy	**Ragusa**	**5-year survival (%)**	**94.9**	**94.1**	**65.7**	**46.6**	**1.0**	**75.3**	**73.9**
		Frequency (%)	22.1	17.1	34.6	7.8	6.0	12.4	100
France	**Bas-Rhin, Côte d'Or, Hérault, Isère**	**5-year survival (%)**	**100.0**	**93.7**	**80.1**	**60.5**	**8.1**	**72.9**	**86.0**
		Frequency (%)	39.4	16.4	31.8	3.4	5.6	3.4	100
France	**Tarn, Somme, Calvados, Doubs**	**5-year survival (%)**	**97.0**	**86.0**	**77.2**	**59.3**	**13.8**	**64.8**	**78.5**
		Frequency (%)	28.2	17.5	30.4	6.6	5.9	11.4	100
Spain	**Granada**	**5-year survival (%)**	**98.4**	**81.7**	**65.8**	**62.7**	**46.5**	**47.2**	**71.6**
		Frequency (%)	10.6	26.3	42.5	8.9	5.0	6.7	100
Estonia		**5-year survival (%)**	**97.8**	**87.8**	**73.3**	**23.1**	**12.0**	**40.2**	**66.4**
		Frequency (%)	8.5	25.0	39.3	12.9	8.0	6.3	100
UK	**Thames**	**5-year survival (%)**	**95.0**	**88.1**	**68.2**	**55.9**	**25.0**	**75.8**	**73.3**
		Frequency (%)	17.9	14.1	20.9	5.3	10.6	31.2	100
UK	**Mersey**	**5-year survival (%)**	**100.0**	**76.8**	**77.0**	**67.8**	**45.2**	**79.9**	**83.4**
		Frequency (%)	33.8	22.4	21.5	9.1	5.9	7.3	100
NL	**Eindhoven**	**5-year survival (%)**	**93.7**	**76.2**	**74.6**	**50.7**	**16.2**	**92.9**	**76.0**
		Frequency (%)	32.4	19.5	31.8	9.2	5.9	1.2	100
All women		**5-year survival (%)**	**97.5**	**87.0**	**76.5**	**54.6**	**18.4**	**68.5**	**79.4**
		Frequency (%)	28.9	18.6	31.0	6.8	6.2	8.5	100

Isère. In Florence (Italy) and Eindhoven (Netherlands), screening programmes started soon after the period of eligibility for our study.[13]

Most patients (90%; range 75–93%) were treated surgically; the lowest percentages were those for Estonia (75%) and Thames (UK) (83%). Mersey (UK), Granada (Spain) and Ragusa (Italy) also had low percentages of surgery (all 88%).

Axillary dissection was performed most often in the Italian and French registry areas (80–90% of cases), and in Eindhoven (Netherlands: 87%). Ten or more lymph nodes were examined in 59% of cases overall, with the highest proportions in Granada (Spain) and Italy (71–83%), and the lowest in Estonia (only 3%). In the UK, only 50% of women underwent axillary lymphadenectomy, and the number of nodes examined was low.

Overall, 2.9% of patients were lost to follow-up, ranging from 1% or less (Italy, Netherlands, UK) to 5–6% in France.

Early, node-negative cancers accounted for 29% of all cases (Table II), ranging from 8.5% in Estonia to 39.4% in France (Bas-Rhin, Côte d'Or, Hérault and Isère). In 8.5% of cases overall, the stage at diagnosis was unknown or could not be reconstructed from available clinical notes, with the highest percentage in Thames (31%).

Relative survival varied widely between these European populations, as has been reported in previous EUROCARE studies.[1,2] Five-year survival ranged from 66% in Estonia to 86% in the French regional group of Bas-Rhin, Côte d'Or, Hérault and Isère (Table II). Survival was generally related to stage distribution, in that areas with a higher proportion of breast cancers diagnosed at earlier stages had better overall survival. In all areas, survival decreased markedly with advancing stage.

Survival within a given category of stage also varied between geographic regions, especially for the more advanced stage categories (Table II). Thus 5-year relative survival for the combined group of women with tumours confined to the breast (T1N0M0 and T2-3N0M0) was 90% or higher for all registries except Granada (Spain) and Eindhoven (Netherlands) (data not shown), whereas for women with node-positive tumours, survival ranged from 66% in Ragusa (Italy) and Granada (Spain) to 80% in France (Bas Rhin, Côte d'Or, Hérault and Isère). Survival was particularly low for locally advanced (T4) cancers in Estonia. The high survival for women with distant metastasis in Granada (Spain) and Mersey (UK) was based only on 9 and 13 cases, respectively. The high 5-year survival in Eindhoven for

women whose disease stage was not specified (93%, Table II) was based on only 7 cases.

Table III shows the results of the multiple regression analysis of relative survival to compare the RER of death between geographic regions, adjusted for age, stage and the number of lymph nodes examined during lymphadenectomy. The simplest model (model 1), including only geographic group and age at diagnosis, provided results closely similar to those from the crude survival analysis. The RER of death was higher than in northern Italy (the reference region) in all regions except the French regional group of Bas-Rhin, Côte d'Or, Isère and Hérault. In 6 of the 7 regions with a high RER, the RER of death was statistically significant.

Further adjustment for disease stage and surgery was incorporated in model 2. The 3 components of stage each emerged as independent prognostic factors, with RER of death strongly and directly related to tumour size (T), the number of metastatic nodes (N) and the presence of metastases (M). Surgical treatment proved to be a significant prognostic factor, even after adjustment for stage. In most regions, the RER of death was lower after adjustment for stage and surgery. Notable exceptions were the French group of Bas-Rhin, Cote d'Or, Hérault and Isère, and Eindhoven (Netherlands), where the risk increased after this adjustment. In both these regions, the proportion of women with early stage disease was higher than in the reference group of northern Italian registries (see Table II). RERs remained significantly higher than in northern Italy (reference region) in 3 areas: Estonia, Eindhoven (Netherlands) and the French group of Tarn, Somme, Calvados and Doubs.

Additional adjustment for the number of axillary nodes examined was incorporated in the last model (model 3, Table III). With this adjustment, which characterises better the extent of nodal involvement, RER of death decreased further in all areas except Granada (Spain), the only region where more nodes were examined than in northern Italy (the reference region). RERs associated with tumour size and metastatic status fell slightly, while the risk associated with nodal status rose slightly in each node-positive category. The number of axillary lymph nodes examined also emerged as an independent prognostic indicator in this model: the

TABLE III – RELATIVE EXCESS RISK (RER) OF DEATH OF WOMEN DIAGNOSED WITH BREAST CANCER IN 1990–1992 FROM SELECTED EUROPEAN REGIONAL GROUPS

	Number of women	Model 1 RER	Model 2 RER	Model 3 RER
Country: regional group				
Italy: Varese, Firenze, Modena	976	1	1	1
Italy: Ragusa	217	1.71*	1.23	1.21
France: Bas-Rhin, Côte d'Or, Hérault, Isère	865	0.84	1.12	1.11
France: Tarn, Somme, Calvados, Doubs	949	1.32*	1.35*	1.33*
Spain: Granada	179	1.72*	1.17	1.18
Estonia	224	2.38*	1.55*	1.50*
UK: Thames	340	1.78*	1.24	1.20
UK: Mersey	219	1.08	1.00	0.96
NL: Eindhoven	509	1.45*	1.73*	1.60*
Age (years)				
<40	296	0.94	1.24	1.24
40–49	797	0.69*	0.82	0.83
50–69	2,155	0.91	1.04	1.04
≥70	1,230	1	1	1
T stage				
T1	1,844		1	1
T2	1,531		2.27*	2.26*
T3	193		3.20*	3.18*
T4	288		3.44*	3.38*
Tx	622		2.95*	2.82*
N stage (no. of metastatic nodes)				
0	2,046		1	1
1	478		1.59*	1.63*
2–3	410		2.06*	2.13*
4–5	209		2.87*	2.98*
6–8	172		3.46*	3.65*
9–12	125		4.08*	4.46*
13+	139		6.42*	7.46*
Clinically N0	497		2.05*	1.70*
Node-positive, no. of nodes unknown	62		3.21*	2.62*
Nx	340		1.65*	1.37
M stage				
M0	4,092		1	1
M+	279		3.81*	3.73*
Mx	107		2.22*	2.19*
Surgery				
No	438		1	1
Yes	4,040		0.32*	0.33*
Number of axillary nodes examined				
Lymphadenectomy not done or not known	1,134			1
1–9	1,215			0.78
10–14	1,120			0.77
15+	1,009			0.66*

*Statistically significant with $p < 0.05$. Tx, Nx, Mx = T, N and M unknown.

RER of death fell with increasing numbers of lymph nodes examined, and was significantly lower in patients with 15 or more nodes examined than in those who did not undergo lymphadenectomy. In all models, the RER for women aged 40–49 years was lower than for all other age groups.

All registries were able to provide information on whether systemic adjuvant radiotherapy, chemotherapy or hormonal therapy was administered. The inclusion of each of these treatment variables in model 3 did not significantly change the overall fit of the model or the RER of any other variables included in the model. When no treatment was the reference category, the RER for chemotherapy was 1.36, that of radiotherapy 0.97 and that of hormonal therapy (mainly tamoxifen) 0.80, which were not statistically significant.

All registries except Eindhoven were able to provide information on whether liver and bone scans had been performed in the staging work-up. Such procedures were frequent in Italy and France (60–80% of all cases) and much lower in other regions (20–50%). The inclusion of these variables in the model resulted in only minor changes in the estimates of RER (data not shown).

We tested several other models to determine the effect of possible interactions between the variables of model 3; however, none modified the pattern of RER by regional group. In particular, an interaction between stage and the duration of follow-up was tested to take into account nonproportionality of the risk of death by time since diagnosis between the various stage categories. This interaction was statistically significant in a model including regional group, age, stage, surgery and the total number of examined nodes, but it did not change substantially the estimates of RER (data not shown).

DISCUSSION

Our analysis shows that the marked differences in survival for breast cancer across Europe, for patients diagnosed in 1990–1991, are mainly due to differences in cancer stage at diagnosis. After adjustment for stage and for the number of axillary nodes examined, as a confounder of staging, survival differences between registries and regions were greatly reduced. However, in 3 of the 9 regional groups, RERs of death remained significantly high even after these adjustments.

Overall 5-year relative survival in Estonia and the 8 regional groups in 5 other countries ranged from 66% to 86%. Geographic variation in stage-specific survival differed notably between early and advanced stage disease. For very early stage disease (T1N0M0), regional differences were small: these tumours are relatively unlikely to have nodal involvement and occult metastases, so whether the work-up is intense or cursory, the result will usually be no nodes or metastases (N0M0). By contrast, the wider regional variation in survival for larger node-negative tumours (T2-3N0M0) may be partly explained by the fact that these tumours have a greater intrinsic probability of regional or distant spread at the time of diagnosis,[11] so the accuracy of staging in patients categorised as (N0M0) will be much more sensitive to the intensity of the work-up. In areas where clinicians do not perform an extensive work-up, many larger tumours categorised as node-negative and free of metastases (T2-3N0M0) may in fact have occult regional or distant spread, while in a region where a more intensive work-up is performed, a greater proportion of these tumours will be truly node-negative and free of metastases.

The probability of finding nodal and distant metastases depends on the diagnostic examinations performed, which in turn depend both on the attitudes and training of the clinicians, and on the availability of appropriate equipment and techniques. The latter will be closely related to the overall affluence of a region.

The number of positive nodes was strongly correlated with the number of nodes examined ($r = 0.74$). UK registries and Estonia, however, which had the highest percentage of cases with pathologic confirmation of lymph node spread (pN+), had the lowest mean number of nodes examined. This suggests that, in these countries, the axillary nodes tend to be examined pathologically only when there is a prior clinical suspicion of nodal involvement, rather than as a routine procedure.

In the multiple regression analysis, adjusting for age (model 1) did not substantially change the relative survival pattern. After the inclusion of stage and surgery, the RER of death in most regions moved towards 1, indicating that stage at diagnosis was a key determinant of regional differences in survival. A further movement of RER towards 1 occurred after adjustment for the number of lymph nodes examined. This procedure improves the adjustment of disease stage in the analysis, because the chance that advanced cases may be misclassified to a less advanced category will be expected to fall as the number of nodes examined increases. Thus, when the number of examined nodes is large, cases classified as node-negative are unlikely to be false negatives, and node-positive cases will include some cases with only minor nodal involvement. The improved adjustment for stage is reflected by a slight increase in the risk of death for each node-positive category, and a low risk for cases with 15 or more nodes examined. In regions where the number of axillary nodes examined was lower than in the reference region, the RER generally fell after adjustment for the number of nodes examined, which suggests that the number of nodes examined should be included in future survival comparisons.

Further adjustments will be necessary in the future to take into account the increasing use of sentinel node sampling.

Patients treated surgically had a significantly lower RER than those not operated on for the same stage and other therapy category (radio-, chemo- and hormono-therapy). We expected the prognostic significance of surgery to decrease when these additional therapies were taken into account (i.e., the RER of surgery should have increased). However, although use of radiotherapy and tamoxifen were associated with a more favourable prognosis, the RER for surgery was not affected by the inclusion of these additional therapies in the multivariable regression model. Practically all patients not treated surgically (10% of total cases) had either advanced or unknown stage tumours, and we propose they were probably considered unlikely to benefit from surgery. According to this interpretation, surgery is a proxy of stage.

We emphasise that only information on whether or not radio-, chemo- and hormono-therapy was performed was available in our study, with no details as to type and dose schedule. It is possible that a favourable prognostic effect of such therapy would be revealed by a more detailed analysis that also considered type and dose.

Women aged 40–49 at diagnosis had the best prognosis of all age groups, as found in other studies.[1,14–16] The persistence of this phenomenon after careful adjustment for stage suggests that it is a biologic phenomenon not simply related to earlier diagnosis.

Adjustment for stage and the number of axillary nodes examined greatly reduced the geographic variation in excess risk. The excess risks for Thames and Mersey (UK) decreased markedly with this adjustment, strongly suggesting that a major reason for the comparatively low survival of breast cancer patients in England, highlighted by the EUROCARE study during the 1980s, was more advanced stage at diagnosis. The results for Thames, however, should be regarded with caution because of the high number cases with unknown stage. The high percentage of cases with unknown stage in this registry has been investigated,[17] and was found to be due to missing information in hospital clinical records.

In 3 regions (Estonia, Eindhoven and the France registries of Tarn, Somme, Calvados and Doubs), the RER of death remained significantly higher than in Northern Italy (reference region). The RER of death fell in Estonia after stage adjustment, but later stage at presentation did not completely explain the excess, indicating that the management of breast cancer patients is not optimal in Estonia. This is consistent with the low survival for most cancers

TABLE IV – RELATIVE EXCESS RISK (RER) OF DEATH BY AGE AT DIAGNOSIS OF WOMEN DIAGNOSED WITH BREAST CANCER IN 1990–1992 FROM SELECTED EUROPEAN REGIONAL GROUPS

Country	Regional group	Under 50 years		50–64 years		65–99 years	
		Number of women	RER	Number of women	RER	Number of women	RER
Italy	Varese, Firenze, Modena	222	1	333	1	421	1
Italy	Ragusa	48	1.86	76	2.23[1]	93	0.70
France	Bas-Rhin, Côte d'Or, Hérault, Isère	203	0.98	294	1.43	368	1.01
France	Tarn, Somme, Calvados, Doubs	233	1.50	346	1.74[1]	370	1.11
Spain	Granada	58	0.79	61	2.32	60	0.75
Estonia		61	1.15	80	2.53[1]	83	1.18
UK	Thames	85	1.86	126	1.72[1]	129	0.88
UK	Mersey	42	1.68	87	1.21	90	0.63
NL	Eindhoven	141	1.36	170	1.64	198	2.02[1]

Risks are adjusted for region, age, stage and staging investigations, surgery (see Table 3). –[1]Statistically significant with $p < 0.05$.

in Estonia in relation to low socioeconomic level.[18–21] Although 5-year survival of locally advanced and metastatic cases in Estonia was especially low, cases diagnosed at an early stage had fairly good survival.

Overall and stage-specific 5-year relative survival in Eindhoven was lower than the average for the study population, and significantly lower than in northern Italy (reference group). The RER of death in Eindhoven increased after adjustment for stage (model 2) because stage distribution was apparently more favourable, but decreased after adjustment for number of nodes examined (model 3) because, on average, fewer nodes were examined than in the reference region. These findings suggest that the low overall and stage-specific survival in Eindhoven might be due to less than optimal patient management after diagnosis, although the available information indicated fairly good adherence to protocols;[22–24] a different distribution of tumour biology cannot be excluded.[25] Only 40% of women over 50 in Eindhoven received tamoxifen as adjuvant therapy, less than the average for the whole study population, but similar to that in the reference region.[3] Women in Eindhoven had a higher proportion of early stage cancers (T1N0M0 and T2-3N0M0) than in most regions, but with lower stage-specific survival rates than in all the other regional groups, which may indicate some underestimation of the extent of the disease. This is supported by the fact that the average number of lymph nodes examined in Eindhoven was also low, and the RER of death decreased substantially after adjustment for this variable. Further, among small tumours (pT1, less than 2cm), the percentage of very small tumours (pT1a, less than 0.5 cm) in Eindhoven was lower (2.3%) than in France (6.0%) or Italy (3.3%).

The RER of death in the French group of Tarn, Somme, Calvados and Doubs was higher than in northern Italy (reference) and the other French group of Bas-Rhin, Côte d'Or, Hérault and Isère. The registries of Somme and Doubs had the highest percentage of cases of unknown stage in this group. The survival of cases for which information on stage is not available may not be representative of the survival of all cases, and this could bias stage-adjusted survival comparisons if such cases constitute a high proportion of the total. When we excluded Somme and Doubs from the analysis, the differences in RER between the 2 French groups narrowed.

In Ragusa (Italy) and Granada (Spain), 2 regions with relatively low socioeconomic level, survival was low for several TNM categories, suggesting that the availability of appropriate diagnostic and treatment modalities was far from optimal.[26]

Breast cancer screening was introduced during the early 1990s in many European countries.[13] Screening is usually offered to women aged 50 and over (50–64 in UK, 50–64 or 50–69 in France in the study period). The implementation of a screening programme, however, may influence the proportion of tumours diagnosed at an earlier stage at any age, because population screening requires the establishment of appropriate structures for diagnosis and treatment that benefit the entire population. Adjustment for stage, however, is expected to take into account the effect of lead time that can arise as a result of both mass (organised) and opportunistic screening. For the French registries of Bas-Rhin, Hérault and Isère, and both UK registries, mass screening activity had begun in the territories they cover at the end of the 1980s, before the period of diagnosis covered by our study. One might expect, therefore, that patients diagnosed in the study period in these areas would include a higher proportion with slow-growing tumours that would later have been diagnosed clinically if not detected at the first round of screening (length-biased sampling). In the UK, however, the first round of screening was not terminated until well after 1991, particularly in some Thames areas, suggesting that this bias is unlikely to be major. In the French registries where screening was in force, the incidence of breast cancer was stable from 1989 to 1991,[27] suggesting that the effect of screening on the detection of slow-growing cancers was already over when the cases were sampled for our study (1990 incidence).

Any screening effect on survival should be confined to (or more marked for) women diagnosed in the age range 50–64 years. To explore this potential bias, we examined the RER of death separately for women aged under 50, 50–64 and 65 or more, adjusting for stage, surgery and the number of examined nodes (see Table IV). In the French regional group where screening was in place (Bas-Rhin, Hérault and Isère), the stage-adjusted RER was actually higher for women offered screening (aged 50–64 years) than for younger or older women (Table IV). In both UK regions, the RER for women aged 50–64 was intermediate between that for younger and older women. These results do not support the argument that screening activity influenced the stage-adjusted comparison of survival between regions. The low RER for women aged under 50 is also be related to the good prognosis of women aged 40–49.

It is noteworthy that full adjustment for stage completely explained the excess death risk for the oldest patients in the UK, seen for women diagnosed during 1978–1985.[1] This more favourable stage-adjusted prognosis may be related to the wide use of tamoxifen in the UK.[3] In Eindhoven, on the contrary, where tamoxifen was less widely used, the highest RER was found in the oldest age group.

In order to reduce geographic differences in breast cancer survival, and to bring regions with poorer survival up to those with the best, the most important public health intervention would be to ensure that health services have adequate facilities for prompt diagnosis of disease, and that all citizens have equal access to those facilities. For many populations, this conclusion likely remains valid today. Persistent geographic differences in the risk of death, despite careful adjustment for the stage of disease at diagnosis, suggests that some European regions provided less than optimal treatment for breast cancer patients. Since the early 1990s, however, methods of diagnosis and treatment of breast cancer have changed markedly, and adherence to protocols has improved. Further studies will be needed to monitor the impact of these changes on survival and the probability of curing breast cancer patients.

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